CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074677

Trade Name : CAPTOPRIL TABLETS USP

Generic Name: Captoptil Tablets USP 12.5mg, 25mg, 50mg and 100mg

Sponsor : Stason Industrial Corp.

Approval Date: May 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074677

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Bioequivalence Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074677

APPROVAL LETTERS

ANDA 74-677

MAY 30 1997

Stason Industrial Corporation
Attention: Min-Liang Pan, Ph.D.
11 Morgan
Irvine, CA 92718-2005

Dear Madam:

This is in reference to your abbreviated new drug application dated June 2, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Captopril Tablets USP, 12.5 mg, 25 mg, 50 mg and 100 mg.

Reference is also made to your amendments dated February 20, December 12, March 3, and May 6, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Captopril Tablets USP, 12.5 mg, 25 mg, 50 mg and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Capoten® Tablets 12.5 mg, 25 mg, 50 mg and 100 mg, respectively, of Bristol Myers Squibb). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

- 5/30/97

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074677

FINAL PRINTED LABELING

302

EXP:

LOT:

APPROVED

Keep tightly closed (protect from moisture). Dispense in a tight container. Do not store above 86° F. NDC 62033-1014-1

Manufactured for:
BOSCOGEN™, INC.
Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

500 Tablets NDC 62033-1014-1

100 mg

CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:

100mg Captopril

Usual Dosage: See package outsert

EXP:

LOT:

Keep tightly closed (protect from moisture).
Dispense in a tight container. Do not store
above 86° F. NDC 62033-1014-0

Manufactured for:
BOSCOGEN™, INC.
Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN , INC.

100 Tablets NDC 62033-1014-0

100 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits
dispensing without prescription.

Each Tablet Contains:

100mg Captopril

Usual Dosage: See package outsert

3 62033 10140 7

277

EXP:

LOT:

Keep tightly closed (protect from moisture). Dispense in a tight container, Do not store above 86° F. NDC 62033-1013-2

Manufactured for:
BOSCOGEN™, INC.
Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

1000 Tablets NDC 62033-1013-2

50 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:

50mg Captopril

Usual Dosage: See package outsert

3 62033 10132 2

EXP:

LOT:

Keep tightly closed (protect from moisture). Dispense in a tight container. Do not store above 86° F. NDC 62033-1013-0

Manufactured for:
BOSCOGEN™, INC. Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made In USA

BOSCOGEN™, INC.

100 Tablets NDC 62033-1013-0

50 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
50mg Captopril
Usual Dosage: See package outsert

3 62033 10130 8

253

EXP:

LOT:

Keep tightly closed (protect from moisture). Dispense in a tight container. Do not store above 86° F. NDC 62033-1012-2

Manufactured for:
BOSCOGEN™, INC.
Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

1000 Tablets NDC 62033-1012-2

25 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:

25mg Captopril

Usual Dosage: See package outsert

3 62033 10122 3

EXP
LOT

Keep tightly closed (protect from moisture). Dispense in a light container. Do not store above 86° F. NDC 62033-1012-0

Manufactured for:
BOSCOGEN™, INC. Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

100 Tablets NDC 62033-1012-0

25 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
25mg Captopril
Usual Dosage: See package outsert

3 62033 10120 9

229

EXP.:

LOT:

Keep tightly closed (protect from moisture). Dispense in a tight container. Do not store above 86° F. NDC 62033-1011-2

Manufactured for:
BOSCOGEN™, INC.
Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

1000 Tablets NDC 62033-1011-2

12.5 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:

12.5mg Captopril

Usual Dosage: See package outsert

3 62033 10112 4

EXP:
LOT:

Keep tightly closed (protect from moisture). Dispense in a tight container. Do not store above 86° F. NDC 62033-1011-0

Manufactured for:
BOSCOGEN™, INC. Irvine, CA 92718
By: Stason Pharmaceuticals, Inc.
Irvine, CA 92718

Made in USA

BOSCOGEN™, INC.

100 Tablets NDC 62033-1011-0

12.5 mg
CAPTOPRIL TABLETS, USP

Caution: Federal law prohibits dispensing without prescription.

Each Tablet Contains:
12.5mg Captopril
Usual Dosage: See package outsert

3 62033 10110 0

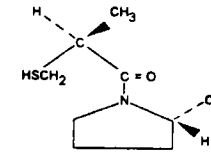
CAPTOPRIL TABLETS, USP

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, captopril should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline [MW 217.29] and has the following structural formula:



Molecular Formula: $C_9H_{15}NO_3S$

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

Each tablet, for oral administration, contains either 12.5, 25, 50, or 100 mg captopril. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, lactose monohydrate, and stearic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase", and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

[1,3]

Pharmacokinetics

After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent.—In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

[1,2]

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated. These hemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy. Placebo controlled studies of 12 weeks duration in patients who did not respond adequately to diuretics and digitalis show no tolerance to beneficial effects on ETT; open studies, with exposure up to 18 months in some cases, also indicate that ETT benefit is maintained. Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

The Survival and Ventricular Enlargement (SAVE) study was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 2,231 patients (age 21 to 79 years) who survived the acute phase of myocardial infarction and did not have active ischemia. Patients had left ventricular dysfunction (LVD), defined as a resting left ventricular ejection fraction ≤40%, but at the time of randomization were not sufficiently symptomatic to require ACE inhibitor therapy for heart failure. About half of the patients had had symptoms of heart failure in the past. Patients were given a test dose of 6.25 mg oral captopril and were randomized within 3 to 16 days post-infarction to receive either captopril or placebo in addition to conventional therapy. Captopril was initiated at 6.25 mg or 12.5 mg tid and after two weeks titrated to a target maintenance dose of 50 mg tid. About 80% of patients were receiving the target dose at the end of the study. Patients were followed for a minimum of two years and for up to five years, with an average follow-up of 3.5 years.

Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg for the placebo and captopril groups, respectively. Blood pressure increased slightly in both treatment groups during the study and was somewhat lower in the captopril group (119/74 vs. 125/77 mm Hg at 1 yr).

Therapy with captopril improved long-term survival and clinical outcomes compared to placebo. The risk reduction for all cause mortality was 19% (P=0.02) and for cardiovascular death was 21% (P=0.014). Captopril treated subjects had 22% (P=0.034) fewer first hospitalizations for heart failure. Compared to placebo, 22% fewer patients receiving captopril developed symptoms of overt heart failure. There was no significant difference between groups in total hospitalizations for all cause (2036 placebo; 2036 captopril).

Captopril tablets were well tolerated in the presence of other therapies such as aspirin, beta blockers, nitrates, vasodilators, calcium antagonists and diuretics.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

INDICATIONS AND USAGE

Hypertension: Captopril tablets are indicated for the treatment of hypertension.

In using captopril, consideration should be given to the risk of neutropenia / agranulocytosis (see WARNINGS).

Captopril may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

Captopril is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

Heart Failure: Captopril tablets are indicated in the treatment of congestive heart failure in combination with diuretics and digitalis. The beneficial effect of captopril in heart failure does not require the presence of digitalis, however, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment.

Left Ventricular Dysfunction After Myocardial Infarction: Captopril tablets are indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤ 40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients.

In considering use of captopril tablets, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (see WARNINGS: Angioedema).

CONTRAINDICATIONS

Captopril tablets are contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including captopril) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx, has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of captopril; some cases required medical therapy. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis

Neutropenia (<1000/mm^3) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient.

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6mg/dL, and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 2500 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥ 1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm^3) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.)

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20 percent were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6 percent of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased. In patients with heart failure, reducing the dose of diuretic, if feasible, may minimize the fall in blood pressure.

Hypotension is not *per se* a reason to discontinue captopril. Some decrease of systemic blood pressure is a common and desirable observation upon initiation of captopril treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within two months.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

[4]

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function

Hypertension—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion.

Heart Failure—About 20 percent of patients develop stable elevations of BUN and serum creatinine greater than 20 percent above normal or baseline upon long-term treatment with captopril. Less than 5 percent of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease.

See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.

Hyperkalemia: Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with

CAPTOPRIL TABLETS, USP

Revised 04-29-97 60763-01

ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency, diabetes mellitus, and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or other drugs associated with increases in serum potassium. (See **PRECAUTIONS: Information for Patients and Drug Interactions**; **ADVERSE REACTIONS: Altered Laboratory Findings**.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Valvular Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction as others.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hemodialysis

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. (See **WARNINGS: Anaphylactoid Reactions During Membrane Exposure**).

Information for Patients

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See **WARNINGS: Angioedema.**)

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See **PRECAUTIONS: General** and **Drug Interactions**; **ADVERSE REACTIONS.**)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that captopril should be taken one hour before meals (see **DOSAGE AND ADMINISTRATION**).

Pregnancy. Female patients of childbearing age should be told about the consequences of second-and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position, and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

Inhibitors Of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction

Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50-kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively.

Studies in rats have revealed no impairment of fertility.

Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50-kg subject. On a body-surface-area basis, these doses are 5 to 25 times maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a body-weight basis (4 to 15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 to 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7 to 200 times MRHD on a body-weight basis (0.6 to 35 times MRHD on a surface-area basis); in monkeys at 20 to 60 times MRHD on a body-weight basis (7 to 20 times MRHD on a surface-area basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20 and 200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surface-area basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on a surface-area basis) for only 5 to 7 days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) on a body-weight basis; 1 to 35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See **WARNINGS: Fetal / Neonatal Morbidity and Mortality.**

Nursing Mothers

Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of captopril to the mother. (See **PRECAUTIONS: Pediatric Use.**)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population: dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

Captopril should be used in pediatric patients only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About one of 100 patients developed proteinuria (see **WARNINGS**).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia / agranulocytosis has occurred (see **WARNINGS**). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction; short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see **WARNINGS** and **PRECAUTIONS [Drug Interactions]** for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See **WARNINGS: Angioedema** and **PRECAUTIONS: Information for Patients.**)

Cough: Cough has been reported in 0.5 to 2% of patients treated with captopril in clinical trials (see **PRECAUTIONS: General, *Cough***).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a whole: Anaphylactoid reactions (see **WARNINGS: Anaphylactoid and Possibly Related Reactions** and **PRECAUTIONS: Hemodialysis**).

General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: Pancreatitis, glossitis, dyspepsia.

Hematologic: Anemia, including aplastic and hemolytic.

Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic: Symptomatic hyponatremia.

Musculoskeletal: Myalgia, myasthenia.

Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: Blurred vision.

Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Altered Laboratory Findings

Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see **PRECAUTIONS**).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE

Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION

Captopril tablets should be taken one hour before meals. Dosage must be individualized.

Hypertension—Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting captopril.

The initial dose of captopril is 25 mg bid or tid. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg bid or tid. Concomitant sodium restriction may be beneficial when captopril is used alone.

The dose of captopril in hypertension usually does not exceed 50 mg tid. Therefore, if the blood pressure has not been satisfactorily controlled after one to two weeks at this dose, (and the patient is not already receiving a diuretic), a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily), should be added. The diuretic dose may be increased at one- to two-week intervals until its highest usual antihypertensive dose is reached.

If captopril is being started in a patient already receiving a diuretic, captopril therapy should be initiated under close medical supervision (see **WARNINGS** and **PRECAUTIONS [Drug Interactions]** regarding hypotension), with dosage and titration of captopril as noted above.

If further blood pressure reduction is required, the dose of captopril may be increased to 100 mg bid or tid and then, if necessary, to 150 mg bid or tid (while continuing the diuretic). The usual dose range is 25 to 150 mg bid or tid. A maximum daily dose of 450 mg captopril should not be exceeded.

For patients with severe hypertension (e.g., accelerated or malignant hypertension), when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other current antihypertensive medication stopped and captopril dosage promptly initiated at 25 mg bid or tid, under close medical supervision.

When necessitated by the patient's clinical condition, the daily dose of captopril may be increased every 24 hours or less under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of captopril is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with captopril therapy (see **PRECAUTIONS: Drug Interactions**), but the effects of the two drugs are less than additive.

Heart Failure- Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg tid may minimize the magnitude or duration of the hypotensive effect (see **WARNINGS: Hypotension**); for these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg tid. After a dose of 50 mg tid is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg tid. A maximum daily dose of 450 mg of captopril should not be exceeded.

Captopril should generally be used in conjunction with a diuretic and digitalis. Captopril therapy must be initiated under very close medical supervision.

Left Ventricular Dysfunction After Myocardial Infarction- The recommended dose for long-term use in patients following a myocardial infarction is a target maintenance dose of 50 mg tid.

Therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, captopril therapy should be initiated at 12.5 mg tid. Captopril should then be increased to 25 mg tid during the next several days and to a target dose of 50 mg tid over the next several weeks as tolerated (see **CLINICAL PHARMACOLOGY**).

Captopril may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin, beta blockers.

Dosage Adjustment in Renal Impairment-Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Accordingly, for patients with significant renal impairment, initial daily dosage of captopril should be reduced, and smaller increments utilized for titration, which should be quite slow (one-to two-week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. (See **WARNINGS: Anaphylactoid Reactions During Membrane Exposure** and **PRECAUTIONS: Hemodialysis**).

HOW SUPPLIED

Captopril Tablets USP are available as: **12.5 mg tablets** in bottles of 100 (NDC 62033-1011-0) and 1000 (NDC 62033-1011-2). **25 mg tablets** in bottles of 100 (NDC 62033-1012-0) and 1000 (NDC 62033-1012-2). **50 mg tablets** in bottles of 100 (NDC 62033-1013-0) and 1000 (NDC 62033-1013-2). and **100 mg tablets** in bottles of 100 (NDC 62033-1014-0). Bottles contain a desiccant-charcoal canister.

The 12.5 mg tablet is a convex-faced diamond with a bisect bar. One side is embossed with "10 | 11" and the other side with "STASON". The 25 mg tablet is a convex-faced diamond with a quadrisect bar. One side is embossed with " 10 X 12" and the other side with "STASON". The 50 mg tablet is a convex-faced diamond with a bisect bar. One side is embossed with "10 | 13" and the other side with "STASON". The 100 mg tablet is a convex-faced capsule-shaped tablet with a bisect bar. One side is embossed with "10 | 14" and the other side with "STASON".

All captopril tablets are white and may exhibit a slight sulfurous odor.

Storage

Do not store above 30°C (86° F). Dispense in a tight container. Keep bottles tightly closed (protect from moisture).

CAUTION: Federal law prohibits dispensing without prescription.

Captopril tablets are manufactured for BOSCOGEN™, INC., Irvine, CA 92718, by Stason Pharmaceuticals, Inc., Irvine, CA 92718.

Revised 04-29-97 60763-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074677

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.3

2. ANDA # 74-677

3. NAME AND ADDRESS OF APPLICANT
Stason Industrial Corporation
Attention:Min-Liang Pan, Ph.D.
11 Morgan
Irvine, CA 92718-2005

4. LEGAL BASIS FOR SUBMISSION
patent expired on 8/8/95
use patent expired on 9/23/96

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Captopril, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FDA:11/6/96: NA letter issued.

Firm:
6/2/95 Orig.submission
12/12/96 Response to 11/6/96 def.letter (This review).
12/16/96 New corr.
3/3/97 Amendment (Labeling)
5/6/97 Amendment (Labeling)

10. PHARMACOLOGICAL CATEGORY
antihypertensive agent

11. Rx

12. RELATED IND/NDA/DMF(s) see # 37

18. CONCLUSIONS AND RECOMMENDATIONS NA major
Approval

19. REVIEWER:
J.Fan

DATE COMPLETED:
1/23/97
5/15/97 (Revised)

cc: ANDA 74-677
DUP Jacket
Division File

Endorsements:

HFD-623/J.Fan 5/15/97; 5/16/97.
HFD-623/V.Sayeed, Ph.D.
X:\NEW\FIRMSNZ\STASON\LTRS&REV\74677N3.D

F/T by

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074677

BIOEQUIVALENCE REVIEW(S)

ANDA 74-677

Stason Industrial Corporation
Attention: Min-Liang Pan, Ph.D.
11 Morgan
Irvine CA 92718-2005

FEB 24 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Captopril Tablets USP, 12.5 mg, 25 mg, 50 mg and 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 19 1997

Captopril Tablets
12.5, 25, 50, and 100 mg
ANDA #74-677
Reviewer: Kuldeep R. Dhariwal
File name: 74677SDW.296

Stason Industrial
Corporation
11 Morgan Drive
Irvine CA 92718
Submission Date:
February 20, 1996

Response to Review of Bioequivalence Study, Dissolution Data, and Waiver Request

Background:

The firm submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its captopril tablets, 100 mg with Squibb's Capoten® tablets, 100 mg. The firm also requested waivers of *in vivo* bioequivalence study requirements for its 12.5, 25, and 50 mg tablets (File name: 74677SDW.695).

The bioequivalence study conducted by the firm was found incomplete by the Division of Bioequivalence. The deficiency comments were sent to the firm on January 31, 1996. The firm submitted the response as amendment on February 20, 1996 which was received by Office of Generic Drugs on February 21, 1996 and assigned to this reviewer on **January 28, 1997**.

Response:

1. Comment 1: **Please submit all statistical analyses (ANOVA analysis) conducted on the test and reference samples (mean) collected at each sampling time.**

Response: The ANOVAs conducted on the plasma captopril concentration at each sampling time are presented. Significant differences between the formulations were observed at 2.50, 4.50, 5.00, 6.00, and 7.00 hours Table 1.

2. Comment 2: **Present the results of blood pressure and heart rate measurements (change from baseline as a function of time) for each subject, as well as the mean data in graphical form, for both test and reference formulations.**

Response: The baseline-uncorrected and baseline corrected systolic blood pressure, diastolic blood pressure, and heart rate measurements of each subject at specified times are tabulated for test and reference formulations. Also, the mean baseline-corrected systolic blood pressure, diastolic blood pressure, and heart rate data are plotted over time for both test and reference formulations (Figures 1-3 attached).

3. Comment 3: **Please provide the criteria for accepting/rejecting a particular run and the Standard Operating Procedures for analytical methods.**

8. Comment 8: **For future studies, we request submission of pharmacokinetic data on diskette (3-1/2" preferred). The diskette should contain the following variables, (in the same order, if possible): Subject number, Period, Sequence, Treatment, C_1-C_{last}, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{½}$, and K_{el}.**

Response: The firm has submitted study diskette containing the requested data.

Comments:

1. According to submitted by the firm, one set of quality control samples (X-low, low, medium, and high) is needed for every treatment or up to 20 clinical samples which is assigned as a "SECTION". The run #29 and 31 consisted of one section and therefore only one set of QC samples were analysed.

The report of conference on "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies" states that QC samples in duplicate at three concentrations (one near the LOQ, one in midrange, and one approaching the high end of the range) should be incorporated into each run. However, this is a guideline and not a requirement for the industries. The agency does not have a regulation about number of quality control samples to be run along with study samples. Therefore, run #29 and 31 with one set of QC samples are acceptable.

2. The firm describes the following sampling and storage

3. The firm has answered to all the stated deficiencies.

4. The bioequivalence study is acceptable. The 90% confidence intervals are within 80-125% for log transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The comparative dissolution testing data for the four strengths of the test products meet the USP specifications of NLT (Q) in 20 minutes.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Stason Industrial Corporation on its Captopril tablets 100 mg, lot #PJ4002F, comparing it to the reference product Capoten® tablets 100 mg, lot #B4J81A, manufactured by Squibb has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Stason Industrial's Captopril 100 mg tablet is bioequivalent to the reference product Capoten® 100 mg tablet manufactured by Squibb.

2. The dissolution testing data on the test product are acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus I (basket) at 50 rpm. The test products should meet the following specifications:

> Not less than (Q) of the labeled amount of captopril in the dosage form is dissolved in 20 minutes.

3. The firm's 12.5 mg, 25 mg, and 50 mg tablets are proportionally similar in their active and inactive ingredients to the 100 mg strength which underwent the acceptable bioequivalence study. The dissolution profiles of all strengths of the test products are similar to their respective strengths of the reference products. The waiver of *in vivo* bioequivalence study requirements for the firm's 12.5 mg, 25 mg, and 50 mg tablets is granted.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

2/18/97

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

Table 1

Mean Captopril Plasma Concentration (ng/mL) and Pharmacokinetic Parameters (N=28): Arithmetic Means and Standard Deviation (SD)

Time (h)	Test		Reference		Test/Ref	Significance at p=0.05
	Mean	SD	Mean	SD		
Plasma Concentrations						
0	0.00		0.0			
0.25	263.12	267.56	264.69	219.64	0.99	NS
0.50	954.79	475.74	864.82	450.17	1.10	NS
0.75	1155.36	614.95	992.75	304.73	1.16	NS
1.00	772.50	253.30	744.50	225.05	1.04	NS
1.25	591.11	237.06	567.89	192.21	1.04	NS
1.50	410.71	157.09	384.36	121.19	1.07	NS
1.75	284.04	95.25	260.25	77.56	1.09	NS
2.00	195.82	58.59	177.78	55.83	1.10	NS
2.50	109.81	32.41	97.46	27.42	1.13	0.0218
3.00	70.58	17.39	67.29	21.59	1.05	NS
3.50	47.34	10.71	45.08	14.69	1.05	NS
4.00	33.04	8.35	31.10	8.38	1.06	NS
4.50	27.03	6.97	24.90	6.54	1.08	0.0317
5.00	21.43	5.39	19.65	4.90	1.09	0.0139
6.00	15.68	4.65	14.45	3.72	1.08	0.0124
7.00	11.44	2.82	10.50	3.22	1.09	0.0243
8.00	8.26	2.11	7.91	2.53	1.04	NS
10.00	5.57	1.42	5.37	1.52	1.04	NS
Pharmacokinetic Parameters						
AUC_{0-t} (ng/mLxh)	1386	387	1276	297	1.09	
AUC_{0-inf} (ng/mLxh)	1409	391	1300	301	1.08	
C_{max} (ng/mL)	1213	609	1079	390	1.12	
T_{max}(h)	0.74	0.19	0.70	0.16	1.06	
$T_{\frac{1}{2}}$(h)	2.78	0.48	2.95	0.69	0.94	
KELM (h^{-1})	0.26	0.04	0.25	0.04	1.04	

KELM: Terminal elimination constant

Table 2

Captopril Plasma Concentrations: Pharmacokinetic Parameters
Least Square Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	1386.4±36.4	1276.3±36.4	1.09	
AUC_{0-inf} (ng/mLxh)	1409.0±36.7	1299.6±36.7	1.08	
C_{max} (ng/mL)	1212.9±78.1	1079.4±78.1	1.12	
$LNAUC_{0-t}$	7.20±0.026	7.13±0.026	1.01	101.2-114.7
$LNAUC_{0-inf}$	7.22±0.026	7.14±0.026	1.01	101.1-114.4
LNC_{max}	7.01±0.050	6.93±0.050	1.01	96.26-122.7

MEAN CAPTOPRIL SYSTOLIC BLOOD PRESSURE

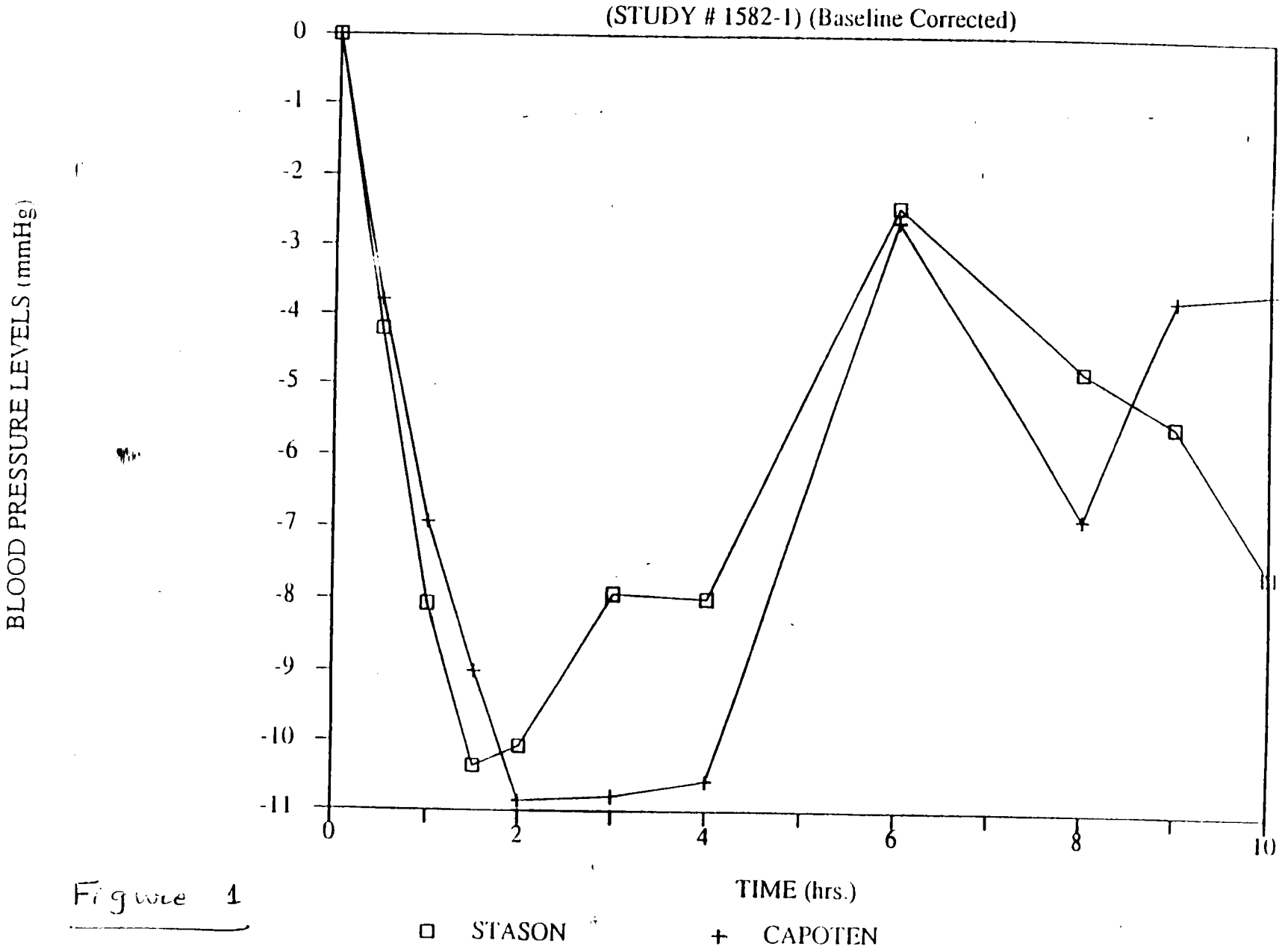


Figure 1

MEAN CAPTOPRIL DIASTOLIC BLOOD PRESSURE

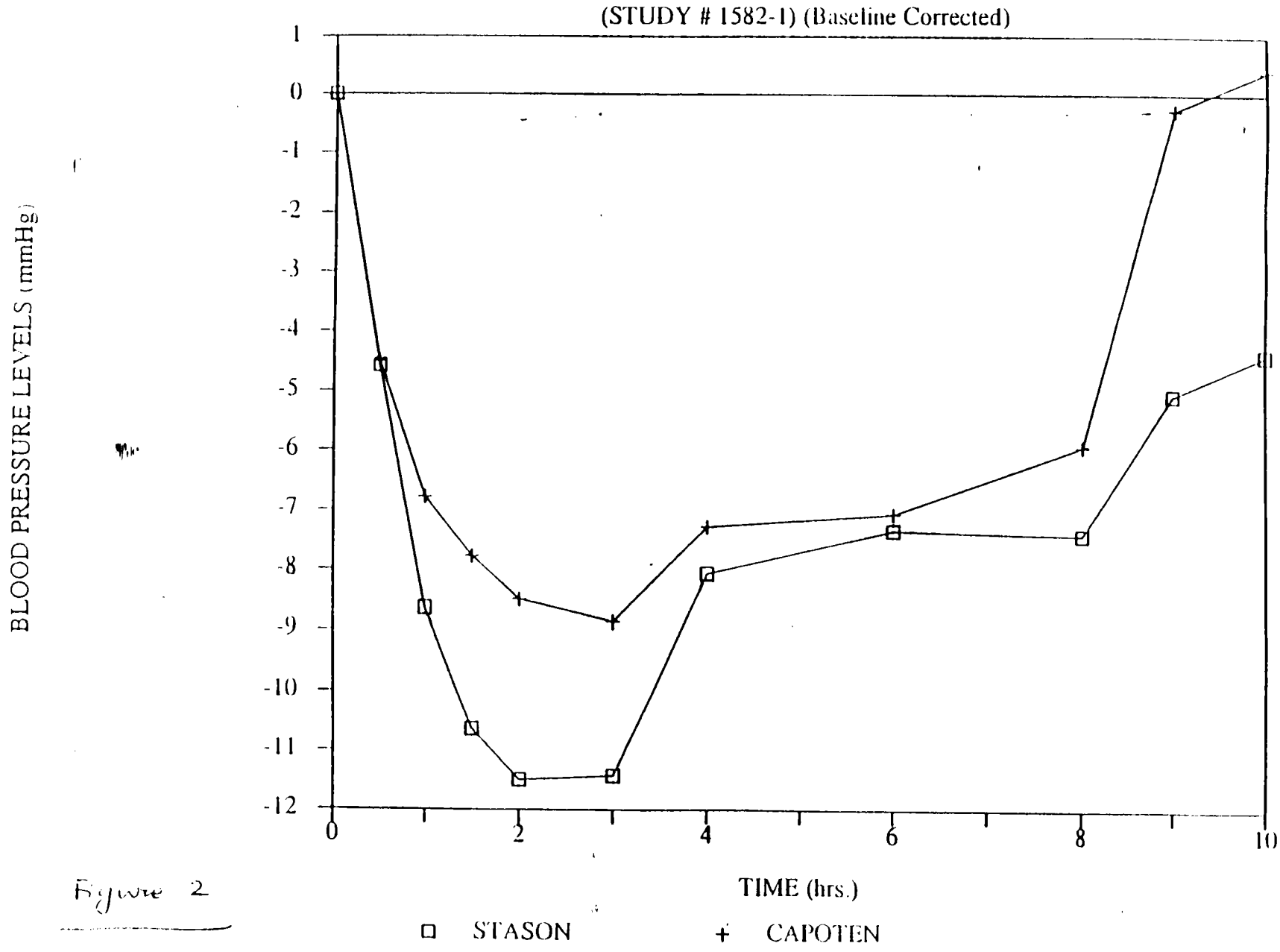


Figure 2

MEAN CAPTOPRIL HEART RATE LEVELS

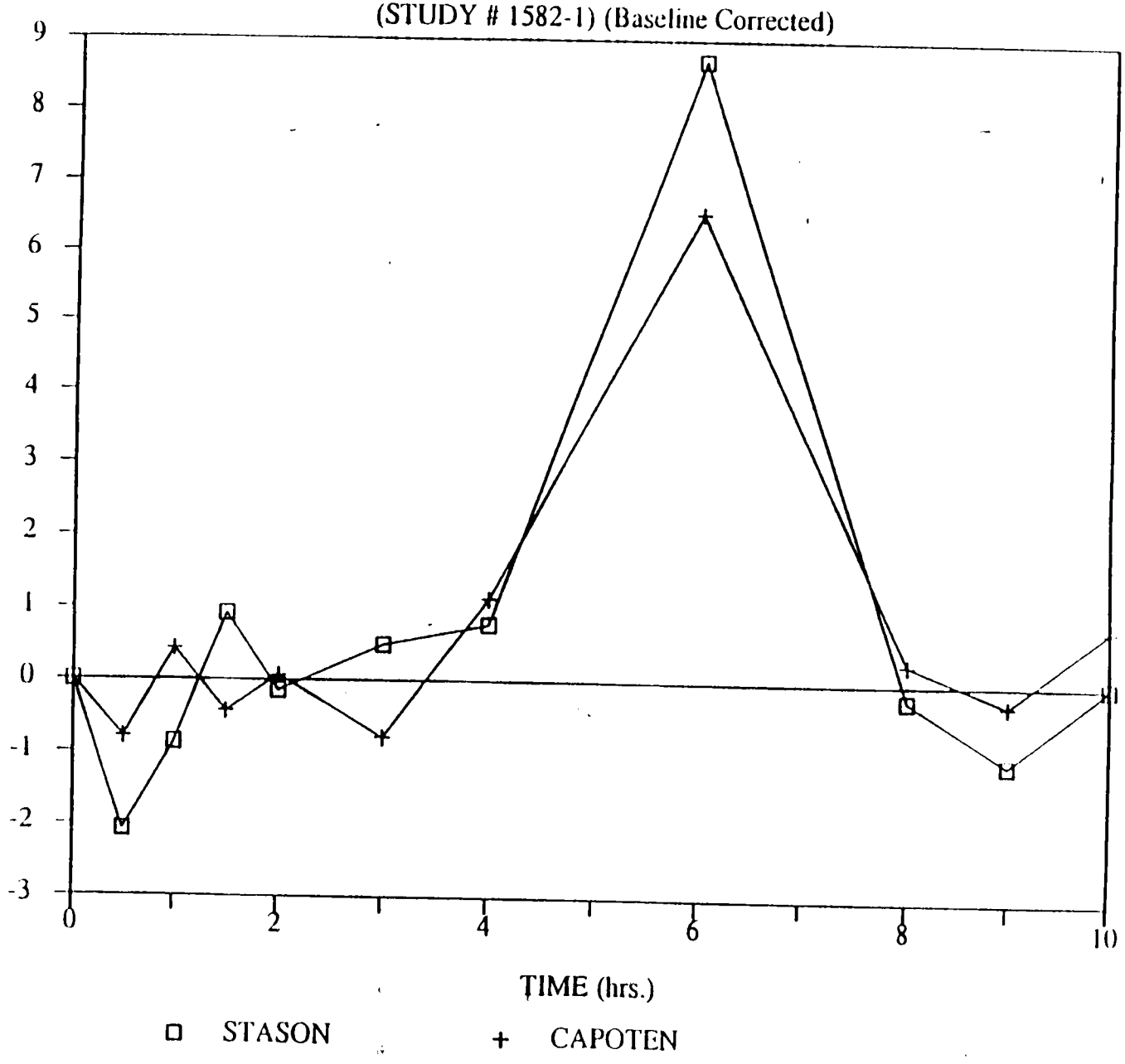


Figure 3

JAN 19 1996

Captopril Tablets
12.5, 25, 50, and 100 mg
ANDA # 74-677
Reviewer: Kuldeep R. Dhariwal
File Name: 74677SDW.695

Stason Industrial
Corporation
11 Morgan Drive
Irvine, CA 92718
Submission Date:
June 2, 1995

Review of Bioequivalence Study, Dissolution Data, and Waiver Request

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its captopril tablets, 100 mg with Squibb's Capoten® tablets, 100 mg. The firm has also requested waivers of *in vivo* bioequivalence study requirements for its 12.5, 25, and 50 mg tablets. To support the request, the firm has submitted comparative dissolution profiles on 12.5, 25, and 50 mg strengths of its product and reference listed drug Capoten®.

Introduction:

Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. It is an antihypertensive and angiotensin converting enzyme (ACE) inhibitor. This enzyme converts angiotensin I, an inactive decapeptide, to angiotensin II, a potent endogenous vasoconstrictor.

After oral administration, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%, it is therefore labeled to be dosed one hour before meals. Approximately 25 to 30% of the circulating drug is bound to plasma proteins. The elimination half-life of captopril is about 2 hours. About 40-50% of the excreted drug in the urine is unchanged captopril.

The reference product is Capoten® by Squibb and is available in four strengths: 12.5, 25, 50, and 100 mg. Its dosage must be individualized.

Bioavailability of Captopril 100 mg Tablets Under Fasting Conditions:

A. Objective:

The objective of this study is to compare the single-dose bioavailability of Stason Industrial Corporation and Squibb (Capoten®) 100 mg captopril tablets under fasting conditions.

B. Study Sites and Investigators:

Clinical Site:

Analytical Site:

Medical Director and Principal Investigator:

Study Director:
Medical Associate:
Protocol #1582-1: A two-way, open-label, single dose, fasting bioavailability study of captopril 100 mg tablets in normal, healthy, non-smoking male volunteers
The protocol was approved by the Institutional Review Board of (page 200, vol. 1.1)
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 177 (vol. 1.1)
Study Dates: Phase I April 23, 1995
Phase II April 30, 1995
Analysis Dates: May 5 to May 17, 1995

C. Study Design:

The study was designed as a single-dose, open-label, randomized, two-way crossover design. The study was executed in two phases with a seven days washout period between drug administrations. The subjects were housed in the clinic at 9 p.m of the evening prior to each drug administration and until the final 10.0 hour post-drug blood draw of each study phase. The subjects were assigned to two groups at random as follows:

Sequence	Subject number	Phase I	Phase II
1	3,4,6,7,11,12,15,16,19,22,23,24,25,26	A	B
2	1,2,5,8,9,10,13,14,17,18,20,21,27,28	B	A

A: Captopril Tablets, 1x100 mg, Stason Industrial Corporation; Lot# PJ4002F; Lot size: tablets; Manufacture Date: 10/24/94; Assay: 104.6%; Content Uniformity: 106.6%

B: Capoten® Tablets, 1x100 mg, Squibb; Lot# B4J81A; Expiration Date: 4/99; Assay: 102.1%; Uniformity of dosage units:

The subjects fasted for ten hours prior to drug administration and until 4.5 hours post-dose. Water was freely allowed except within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects remained ambulatory for the first hour following drug administration. At 4.5 and 9.5 hours postdrug administration, standardized, xanthine-free meals, including a non-caffeine containing beverage were provided to all subjects. Identical meals were served during both housing periods. Blood pressure and heart rate were monitored during each study phase at 0,0.5,1,1.5,2,3,4,6, and 8 hours post dose. Post-study hematology, clinical chemistry, and urinalysis testing was done on all subjects.

D. Subject Selection:

Twenty-eight normal, healthy, non-smoking male volunteers were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±10% from ideal weight for height as determined by the Table of Desirable Weights for Men (Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980)
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from the study based on the following criteria:

- known history of hypersensitivity to captopril or related drugs
- known history or presence of cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs
- known history of asthma, chronic bronchitis or other bronchospastic condition
- known history of systemic lupus erythematosus, drug dependency, or serious psychological disease
- presence of any significant physical or organ abnormality
- blood donation within previous 60 days
- use of enzyme-inducing and enzyme-inhibiting drugs within 30 days prior to entry into the study
- regular use of medication, abuse of alcoholic beverages, or participation in a clinical trial with an investigational drug within 30 days preceding the study
- positive urine test for drugs of abuse

Subjects were imposed with following restrictions:

- no drugs similar to the one under study or administration of any medication (including over-the-counter preparations) within 14 days preceding entry into the study
- no alcohol consumption for 48 hours prior to each phase of the study
- no xanthine containing foods including tea, coffee, chocolate and cola drinks for 48 hours prior to each phase of the study

E. Sample Collection:

F. Analytical Methods:

G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C_t). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C_t/KE. To calculate the elimination rate constant (KE), regression analyses were performed on the natural log of plasma concentration values versus time. Calculations were based on the most linear portion of the terminal elimination phase as shown in semi-log plots of individual subject data. The KE was taken as the slope multiplied by (-1). All ANOVAs were performed with the SAS General Linear Models Procedure. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05. Based on the pair-wise comparisons of the log transformed AUC and C_{max} data, the relative ratios of the geometric means and the 90% geometric confidence intervals were determined.

H. Results:

1.Clinical:

All twenty-eight subjects who entered the study, completed the study. Blood pressure and heart rate were monitored during each study phase at 0,0.5,1,1.5,2,3,4,6, and 8 hours. The firm has provided the measurements in a tabular form.

Adverse events:

Following subjects experienced adverse events during the study, all of which resolved without any medication:

Subject #	Phase	Product	Sign/Symptom
10	I	ref	headache
20	I	ref	headache
27	I	ref	lightheaded
10	II	test	indigestion
20	II	test	headache
24	II	ref	headache

Post-study laboratory results for all subjects were either considered within the reference range or clinically not significant.

Protocol deviations:

A few deviations from the scheduled phlebotomy time occurred during the study:

Subject #	Phase	Product	Deviation
19	II	ref	0.5 h sample was drawn 1 min. late
20	II	test	0.5 h sample was drawn 1 min. late
4	II	ref	6 h sample was drawn 19 min. early
			8 h sample was drawn 26 min. early

Repeat assays:

2. Analytical:

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of captopril at each time point after test and reference products are shown in Table 1. The plots of the mean plasma captopril levels for the two formulations over the 10 hour sampling period are presented in Figures 1 and 2, in linear and semi-log formats. The arithmetic mean for each parameter is tabulated in Table 1 and the results of the analysis of variance are summarized in Table 2. There is no statistically significant difference between the two formulations for any parameter. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product are about 9% higher than the respective estimates for the reference product. The C_{max} for the test product was 11% higher than that for the reference product and occurred 2 minutes later.
The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Captopril (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
3	1286.75	1307.91	1286.68	1307.85
7	1092.86	1111.60	1092.88	1111.64
24	1281.96	1299.30	1282.00	1299.31

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 3. The test/reference ratio for AUC_{0-t} ranged from (mean 1.097), AUC_{0-inf} ranged from (mean 1.095) and for C_{max} ranged from with a mean of 1.167.

Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.96-0.99 for test and 0.96-0.99 for reference product.

The following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	101.19-114.66	101.19-114.66
$LNAUC_{0-inf}$	101.11-114.41	101.11-114.41
LNC_{max}	96.26-122.67	96.26-122.67

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125. Statistical analysis of the data did not show any significant period or sequence effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}. However, there was statistically significant ($p < 0.05$) treatment effect for AUC_{0-t} ($p=0.0424$) and AUC_{0-inf} ($p=0.0449$). But the p values for $LAUC_{0-t}$ and $LAUC_{0-inf}$ were 0.0529 and 0.0549 respectively for treatment effect.

In Vitro Dissolution Testing:

The firm has submitted comparative dissolution data for test and reference products using USP dissolution method. The dissolution testing was done in 900 mL of 0.1N HCl using apparatus 1 (basket) at 50 rpm. The assay methodology was The 100 mg tablets used in the dissolution tests were from the same lot used in the *in vivo* bioequivalence study. The firm has demonstrated that of the test products are dissolved in 20 minutes. The dissolution profiles for the test and reference products are similar (Table 6).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its captopril 12.5 mg, 25 mg, and 50 mg tablets. The comparative quantitative composition of all strengths are shown in Table 5. The 12.5 mg, 25 mg, and 50 mg tablets are proportionally similar in their active and inactive ingredients to the 100 mg strength. The dissolution profiles of all strengths of the test products are similar to their respective strengths of the reference products (Table 6). All test and reference products dissolve greater than in 20 minutes.

Second source of active ingredient:

The firm has also used another source of active ingredient to manufacture four strengths of captopril tablets. The firm has submitted the dissolution data for these tablets and compared them with the reference product (Table 7). The dissolution data of test tablets manufactured using second source of active ingredient are acceptable.

Comments:

1. All twenty-eight subjects who entered the study, completed the study. Four subjects experienced adverse effects, all of which resolved without any medication. Post-study laboratory results for all subjects were either considered within the reference range or clinically not significant.

2. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product are about 9% higher than the respective estimates for the reference product. The C_{max} for the test product was 11% higher than that for the reference product and occurred 2 minutes later. The 90% confidence intervals for log transformed data for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125.

3. There were no statistical significant period or sequence effects for AUC_{0-t}, AUC_{0-inf}, and C_{max}. However, there was statistically significant ($p < 0.05$) treatment effect for AUC_{0-t} ($p=0.0424$) and AUC_{0-inf} ($p=0.0449$). But the p values for $LAUC_{0-t}$ and $LAUC_{0-inf}$ were 0.0529 and 0.0549 respectively for treatment effect.

4. The dissolution testing was done using USP method. The comparative dissolution testing data for the four strengths of the test products meet the USP specifications of NLT (Q) in 20 minutes. The four strengths of the test products are proportionally similar in their active and inactive ingredients.

5. The firm has also used another source of active ingredient to manufacture four strengths of captopril tablets. The firm has submitted the dissolution data for these tablets and compared them with the reference product (Table 7). The dissolution data of test tablets manufactured using second source of active ingredient are acceptable.

6. **NOT TO BE RELEASED UNDER FOI:** In the present study, following values for elimination rate constant (KEL^{-}) and half-life ($T_{\frac{1}{2}}$) are reported:

Deficiencies:

1. The firm is requested to submit all statistical analyses (ANOVA analysis) conducted on the test and reference samples (mean) collected at each sampling time.

2. The firm is requested to present results of blood pressure and heart rate measurements (change from baseline as a function of time) for each subject as well as the mean data in graphical form for test and reference formulations.

3. The firm should give the criteria for accepting/rejecting a particular run. Also, please provide Standard Operating Procedures (SOP) for analytical methods.

7. The 6 and 8 hour blood samples for subject #4 in phase II were drawn 19 and 26 minutes early, respectively. Which phlebotomy time (actual or scheduled) was used to calculate area under the curve?

8. For future studies, the firm is requested to submit pharmacokinetic data on diskette also.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Stason Industrial Corporation on its captopril tablets, 100 mg, lot #PJ4002F, comparing it to the reference product Capoten® tablets, 100 mg, lot #B4J81A has ben found incomplete by the Division of Bioequivalence for the reasons given in the deficiency.

2. The dissolution testing data on the test product are acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using apparatus I (basket) at 50 rpm. The test products should meet the following specifications:

Not less than of the labeled amount of captopril in the dosage form is dissolved in 20 minutes.

3. The waiver of the *in vivo* bioequivalence study requirements for the firms's 12.5 mg, 25 mg, and 50 mg tablets is denied pending approval of the 100 mg strength of the test product.

4. From the Bioequivalence viewpoint, the firm has met the *in vitro* dissolution requirements, but not the *in vivo* bioequivalence requirements and the application is not approvable.

The firm should be informed of the deficiencies and recommendations.

1/19/96

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
Mean	0.983	0.982
SD (±)	0.640	0.740
CV (%)	0.650	0.760
Range		

Table 5

Comparative Quantitative Composition of Captopril Tablets

Ingredient	% w/w	Strength (mg)			
		12.5	25	50	100
		Amount per tablet (mg)			
Captopril, USP	18.18	12.50	25.00	50.00	100.00
Lactose Monohydrate,NF Microcrystalline Cellulose, NF Starch, NF Stearic Acid, NF					
Total	100.0	68.75	137.5	275.0	550.0

Inactive Ingredients of reference listed drug (Squibb)

Microcrystalline Cellulose
Corn Starch
Lactose
Stearic Acid

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Captopril Tablets
Dose Strength: 100 mg, 50 mg, 25 mg, 12.5 mg
ANDA No.: 74-677
Firm: Stason Industrial Corporation
Submission Date: June 2, 1995
File Name: 74677SDW.695

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 mL
Specifications: NLT (Q) in 20 minutes
Reference Drug: Capoten® Tablets (Squibb)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Min)	Test Product Lot #PJ4002 Strength(mg) 100			Reference Product Lot # B4J81A Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98		3.9	98		1.3
20	102		1.7	98		1.2
30	102		1.5	98		1.2

Sampling Times (Min)	Test Product Lot # PJ4005 Strength(mg) 50			Reference Product Lot # B4J76A Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98		3.6	100		3.4
20	100		2.6	102		1.5
30	100		2.9	102		1.4

Sampling Times (Min)	Test Product Lot # PJ4004 Strength(mg) 25			Reference Product Lot # C4K08A Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	99		4.4	98		3.0
20	100		4.1	100		3.2
30	100		4.1	100		3.3
Sampling Times (Min)	Test Product Lot # PJ4003 Strength(mg) 12.5			Reference Product Lot # B4J63A Strength(mg) 12.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	93		8.0	94		5.9
20	98		3.7	101		3.6
30	97		6.3	100		4.6

Table 7. In Vitro Dissolution Testing
(second source of active ingredient)

Drug (Generic Name): Captopril Tablets
Dose Strength: 100 mg, 50 mg, 25 mg, 12.5 mg
ANDA No.: 74-677
Firm: Stason Industrial Corporation
Submission Date: June 2, 1995
File Name: 74677SDW.695

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 mL
Specifications: NLT (Q) in 20 minutes
Reference Drug: Capoten® Tablets (Squibb)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Min)	Test Product Lot # PL4005 Strength(mg) 100			Reference Product Lot # B4J81A Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
10	94		3.2	97		2.3
20	98		4.8	98		2.0
30	99		3.7	99		1.4

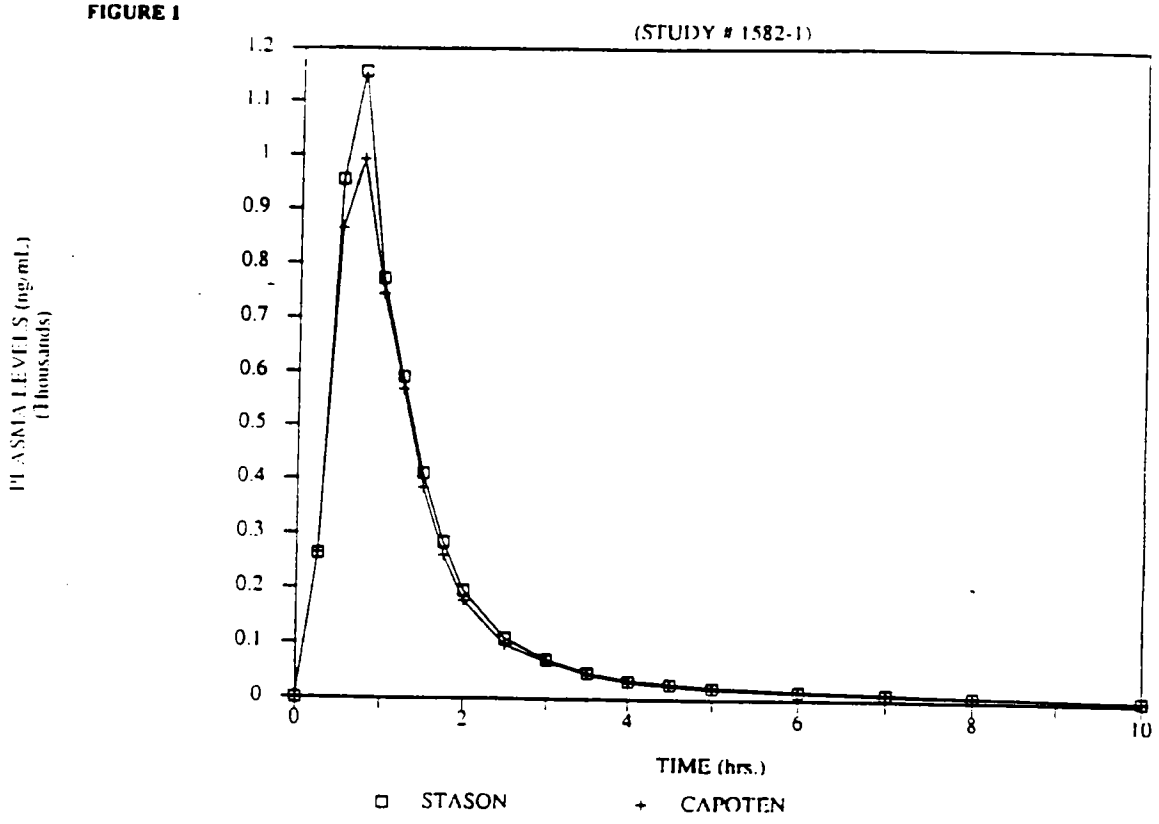
Sampling Times (Min)	Test Product Lot # PL4004 Strength(mg) 50			Reference Product Lot # B4J76A Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97		3.8	100		1.8
20	99		3.0	100		1.6
30	100		3.4	100		1.9

Sampling Times (Min)	Test Product Lot # PL4003 Strength(mg) 25			Reference Product Lot # C4K08A Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97		3.5	94		6.7
20	100		2.8	99		3.3
30	99		2.8	98		3.1

Sampling Times (Min)	Test Product Lot # PL4002 Strength(mg) 12.5			Reference Product Lot # B4J63A Strength(mg) 12.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98		4.5	99		6.1
20	102		2.9	102		3.6
30	101		2.8	101		3.7

MEAN PLASMA CAPTOPRIL LEVELS

FIGURE 1



SEMI-LOG MEAN PLASMA CAPTOPRIL LEVELS

FIGURE 2